Cholesterol turnover and metabolism in two patients with abetalipoproteinemia

DeWitt S. Goodman, Richard J. Deckelbaum, Robert H. Palmer, Ralph B. Dell, Rajasekhar Ramakrishnan, Georges Delpre, Yitzchak Beigel, and Michael Cooper

Departments of Medicine and Pediatrics and the Arteriosclerosis Research Center, Columbia University College of Physicians and Surgeons, New York, NY 10032,[1] Departments of Gastroenterology and Pediatrics, Hadassah University Hospital, Hebrew University-Hadassah Medical School, Jerusalem, Israel,[2] Beilinson Medical Center, Petah Tikva,[3] and Kaplan Hospital, Rohovot, Israel[4]

Abstract Total body turnover of cholesterol was studied in two patients with abetalipoproteinemia, a 32-year-old man and a 31-year-old woman. The patients received [^{14}C]cholesterol intravenously, and the resulting specific activity-time curves (for 40 and 30 weeks, respectively) were fitted with a three-pool model. Parameters were compared with those from studies of cholesterol turnover in 82 normal and hyperlipidemic subjects. A three-pool model gave the best fit for the abetalipoproteinemic patients, as well as for the 82 previously studied subjects, suggesting general applicability of this model. Cholesterol production rates in the two abetalipoproteinemic subjects (0.82 and 0.89 g/day) were close to values predicted for persons of their body weight. Thus, total body turnover rate of cholesterol was quite normal in abetalipoproteinemia, confirming previous reports. Very low values (9.2 and 8.4 g) were found for M_1, the size of the rapidly exchanging compartment pool 1, in the two abetalipoproteinemic subjects. These values were well below the values predicted (from the comparison study population) for normal persons of this size with low plasma cholesterol levels. For one patient, total body exchangeable cholesterol was very low, although not significantly below the predicted values for a person of his size. In the second patient, the observed estimate for total body exchangeable cholesterol was well within the range of values predicted for persons of her size with low to extremely low cholesterol levels. The finding of a normal rate of cholesterol synthesis in abetalipoproteinemia, together with a very small mass of cholesterol in pool 1, suggests that, in normals, a large portion of the exchangeable cholesterol in pool 1 is not involved in the regulation of cholesterol synthesis rates in the tissues that comprise this pool.—**Goodman, D. S., R. J. Deckelbaum, R. H. Palmer, R. B. Dell, R. Ramakrishnan, G. Delpre, Y. Beigel, and M. Cooper.** Cholesterol turnover and metabolism in two patients with abetalipoproteinemia. *J. Lipid Res.* 1983. **24:** 1605–1611.

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Abetalipoproteinemia is a rare genetic disorder characterized by the absence of apolipoprotein B (apoB) and of apoB-containing lipoproteins in plasma (1). Patients with this disease have extremely low levels of plasma cholesterol and triglycerides, and almost completely lack lipoproteins in the density ranges of low density lipoproteins (LDL), very low density lipoproteins (VLDL), and chylomicrons. Plasma lipids are transported almost entirely in high density lipoproteins (HDL) (1–3). Clinical characteristics commonly include fat malabsorption, acanthocytosis, retinitis pigmentosa, and neuromuscular degeneration (1).

A number of investigators have examined whole body cholesterol synthesis rates in patients with abetalipoproteinemia using sterol balance techniques (4–7). Synthesis rates of 15.4 and of 15.2 mg/kg per day were observed in two patients, one studied by Myant, Reichl, and Lloyd (4) and the other by Kayden (5). These values are similar to those seen in normal and hyperlipidemic subjects (4, 8–12). Somewhat elevated rates of cholesterol synthesis were reported by Illingworth et al. for two patients with abetalipoproteinemia (6) and for one patient with homozygous familial hypobetalipoproteinemia (7). The magnitude of the observed increase could be largely accounted for, however, as a compensation for sterol losses that occurred due to intestinal malabsorption. Thus, it is generally agreed that endogenous body cholesterol synthesis is not particularly excessive in abetalipoproteinemia.

These findings were initially surprising. It is now well established that LDL plays a major role in the feedback regulation of cholesterol biosynthesis in cultured human fibroblasts and in many other types of cells, via the LDL receptor pathway (11). Accordingly, it was expected that the LDL receptor pathway would be derepressed in pa-

Abbreviations: apo, apolipoprotein; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; PR, production rate; k, rate constant; M_1, M_2, M_3, pool sizes.

[1] D. S. Goodman, R. H. Palmer, R. B. Dell, and R. Ramakrishnan.
[2] R. J. Deckelbaum.
[3] G. Delpre and Y. Beigel.
[4] M. Cooper.

tients with abetalipoproteinemia, leading to elevated rates of cholesterol synthesis. This did not occur, however, as indicated by both the sterol balance studies cited above, and by studies of Reichl, Myant, and Lloyd (12) with freshly isolated lymphocytes from patients with abetalipoproteinemia.

This apparent paradox was resolved recently by studies of the role of apolipoprotein E (apoE)-containing HDL in abetalipoproteinemia. The mean content of apoE in HDL in abetalipoproteinemia was twice that found in normal subjects (3, 13). Also, abetalipoproteinemic HDL contained more than twice the amount of cholesteryl ester per particle than did normal HDL (3). It was estimated that apoE-rich HDL in abetalipoproteinemia has the capacity to deliver cholesterol to tissues via the LDL receptor pathway equivalent to an LDL cholesterol concentration of 50–150 mg/dl (13). It was concluded that apo-E rich HDL can account for the suppression of cholesterol synthesis and LDL receptor activity previously observed in abetalipoproteinemia.

We now report studies designed to obtain more information about the in vivo parameters of whole body cholesterol metabolism in patients with abetalipoproteinemia. Long-term studies of the turnover of plasma cholesterol were carried out in two abetalipoproteinemic patients, followed by compartmental analysis of the kinetic data. The results provide information about a variety of parameters of body cholesterol metabolism, including the sizes of body pools of exchangeable cholesterol and the rates of body cholesterol turnover, in abetalipoproteinemic patients as compared to normal and hyperlipidemic persons.

METHODS

Patients

Two adult Israeli volunteers with abetalipoproteinemia were studied; written informed consent was obtained from each. The study was approved by the Institutional Review Board of Columbia University College of Physicians and Surgeons in New York, and by the Human Ethics Committee of the Hadassah University Hospital in Jerusalem. The characteristics of the patients are cited in **Table 1.** Both patients had typical clinical findings of abetalipoproteinemia; they have been referred to previously as subjects number 2 and 3 in the studies reported by Blum et al. (13). The subjects maintained their customary low fat diet (15% of total calories), were clinically stable, and did not show significant changes in weight during the course of the studies. Subject 1 received oral vitamin E, 3 g, and vitamin A, 10,000 international units, daily throughout the study; subject 2 received oral vitamin A, 50,000 international units, twice weekly.

TABLE 1. Characteristics of abetalipoproteinemic subjects

	Subject 1	Subject 2
Age (yr)	32	31
Sex	M	F
Weight (kg)	51	64
Height (cm)	161	161
Excess weight (kg)[a]	−7.2	10.8
Serum cholesterol (mg/dl)[b]	44.6 ± 3.2	40.4 ± 5.2
Serum triglyceride (mg/dl)[b]	7.9 ± 4.2	10.8 ± 7.6

[a] Excess weight = observed minus ideal body weight, as defined previously (9).
[b] Mean ± SD values for 33 samples (for subject 1) or for 26 samples (for subject 2) analyzed during the course of the study.

Turnover studies

For each subject, 50 μCi of [4-^{14}C]cholesterol (New England Nuclear, Boston, MA; specific radioactivity 52.5 mCi/mmol) was dissolved in 0.6 ml of acetone, and the acetone solution was then injected slowly, via a 250-μl syringe, beneath the surface of 20 ml of the subject's own serum. Prior to study, the [4-^{14}C]cholesterol had been assayed by thin-layer chromatography for radiochemical purity and had been found to be more than 98% pure. The serum had been freshly drawn the preceding day, and was gently swirled during the period of acetone addition. The labeled serum was shaken gently at 37°C for 3 hr, and was then kept at room temperature an additional 17–18 hr. The serum was then sterilized by passage through a Millipore filter of pore size 0.22 μm.

To conduct the turnover study, labeled serum containing approximately 25 μCi of [4-^{14}C]cholesterol was injected intravenously, and the specific radioactivity of serum total cholesterol was determined in samples collected serially thereafter, as described in detail previously (14, 15). The amount of radioactivity injected into each subject was measured precisely. Samples of venous blood were collected at approximately 0.5, 1, 2, 4, 6, 9, 12, 16, 21, and 26 days after injection, and then at less frequent intervals (first weekly, then every other week) until the end of the study. For subject 1, 34 samples were collected during a period of 40 weeks. For subject 2, 26 samples were collected during a period of 30 weeks. The samples of serum were collected in Israel, and were stored frozen at −20°C until shipped to New York in the frozen state. In New York the sera were thawed and analyzed to determine the specific radioactivity of cholesterol and the serum concentrations of cholesterol and triglyceride in each sample, as described previously (14–16).

Data analysis

The specific radioactivity data were analyzed by a weighted, least-squares technique described before (15, 17), to determine the parameters of a three-pool mam-

millary model which would provide the best fit. The fitting process yields six unique model parameters: PR (cholesterol production rate in g/day); M_1 (size of pool 1 in g), and the constants k_{12}, k_{13}, k_{21}, and k_{31} (rate constants for transfer between pool 2 or 3 and pool 1 in days^{-1}). As discussed previously (15), assumptions regarding the relative rates of synthesis of cholesterol in pools 2 and 3 lead to various estimates of pool size. Minimum values for M_2 and M_3 were computed by assuming that no synthesis occurs in the side pools (i.e., that all of cholesterol production enters pool 1). The sum of these minimum pool size estimates plus the size of pool 1 provided a minimum estimate for total exchangeable body cholesterol (M_{tot} min). Intermediate and maximum values for M_2 and M_3 were calculated as well, as described previously (9).

Comparison study population

The results obtained with the two subjects with abetalipoproteinemia were compared with results obtained from long-term studies (32–49 weeks duration) of the turnover of plasma cholesterol carried out at Columbia-Presbyterian Medical Center during the past decade in 82 normal and hyperlipidemic subjects. Twenty-one subjects were normal, 22 had hypercholesterolemia alone, 25 had hypertriglyceridemia alone, and 14 had both hypercholesterolemia and hypertriglyceridemia (see (9) for definition of terms). The results obtained with the first 54 of these subjects have been reported in full (9). The remaining 28 subjects were studied subsequent to our previous report (9), and will be reported in detail elsewhere.

With the first 54 subjects, an extensive statistical analysis led to the delineation of a set of predictive equations which describe some of the major body cholesterol kinetic parameters (9). These equations related major model parameters to physiological variables of body size, serum lipid levels, and age. These equations accounted for a great deal of the variation found between subjects in the model parameters of PR, M_1, and the minimum values of M_3 and of total body exchangeable cholesterol.

We have recently updated these equations by determining the coefficients that describe the identified relationships between model parameters and physiological variables for the larger study population of 82 subjects. The equations so obtained are given in **Table 2.** All of the multiple correlation coefficients shown are 0.72 or higher, so that the sets of physiological variables shown can account (as r^2) for 53 to 68% of the observed variation in the four model parameters listed. These equations were used to provide comparisons with the results obtained in the abetalipoproteinemic subjects.

RESULTS

Model and model parameters

Fig. 1 and **Fig. 2** show the turnover data obtained with the two abetalipoproteinemic subjects. The solid curve drawn in each figure represents the best fit obtainable with the three exponential equation that describes the three-pool model (15). As described previously (15), the data for each subject were also analyzed to determine the best fit obtainable with a two-pool model and with models containing more than three pools. With both subjects, the three-pool model provided a significantly better fit to the data than did a two-pool model; no further improvement in fit was obtained for either subject with a four-compartment model. Similar findings have been reported previously (9) for 54 normal and hyperlipidemic subjects. On the basis of the previous observations (9) we concluded that the three-pool model appears to be generally valid for the study of cholesterol turnover in humans. The present results extend this conclusion to include severely hypolipidemic subjects with abetalipoproteinemia.

TABLE 2. Equations for major model parameters (82 subjects)

Dependent Variable[a]	Independent Variables[b] and Regression Coefficients	Intercept	Multiple r
PR	0.0213 Wt	−0.386	0.77
M_1	0.291 Wt + 0.0397 Chol − 1.63 TGGP	−6.95	0.82
M_3 min	0.659 Wt + 0.051 Chol + 0.536 Age	−52.1	0.73
M_3 min	0.992 EWt + 0.375 Age	11.0	0.72
M_{tot} min	0.956 Wt + 0.091 Chol	−16.6	0.81
M_{tot} min	1.036 EWt + 0.00106 Chol · Wt	50.0	0.80

[a] PR = production rate (g/day); M_1 = size of pool 1 (g); M_3 min = minimum estimate of the size of pool 3 (g); M_{tot} min = minimum estimate for total body exchangeable cholesterol (g).

[b] Wt = total body weight (kg); EWt = excess body weight (observed weight minus ideal weight, in kg); Chol = serum cholesterol concentration (mg/dl); TGGP = variable equal to 1, 2, or 3 depending on serum triglyceride concentration (<200, 200–300, or >300); age (years); Chol · Wt = serum cholesterol concentration times body weight.

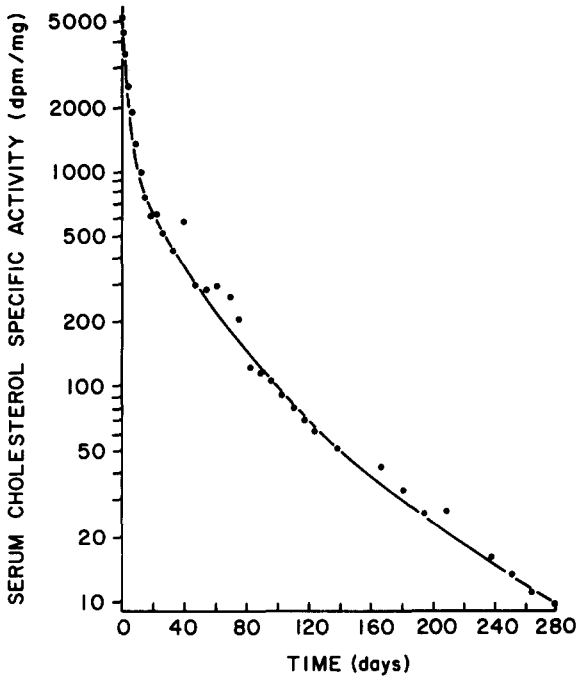

Fig. 1. Turnover of plasma cholesterol in Subject 1.

Although the turnover curves for both abetalipoproteinemic subjects fit the three-pool model, the rate of decline of cholesterol specific radioactivity with time was unusually great. Thus, the specific radioactivity values had declined to 1% of initial values by approximately days 140 and 190 in the two subjects, respectively. In contrast, in 21 normal subjects the die-away curves did not decline to 1% of initial value until 254 ± 38 mean ± SD) days, and in only 1 normal subject was the 1% value reached in less than 200 days. For the comparison study population of 82 subjects, values of 1% of initial values were not reached until 258 ± 76 (mean ± SD) days, with only 3 subjects reaching the 1% value in less than 150 days.

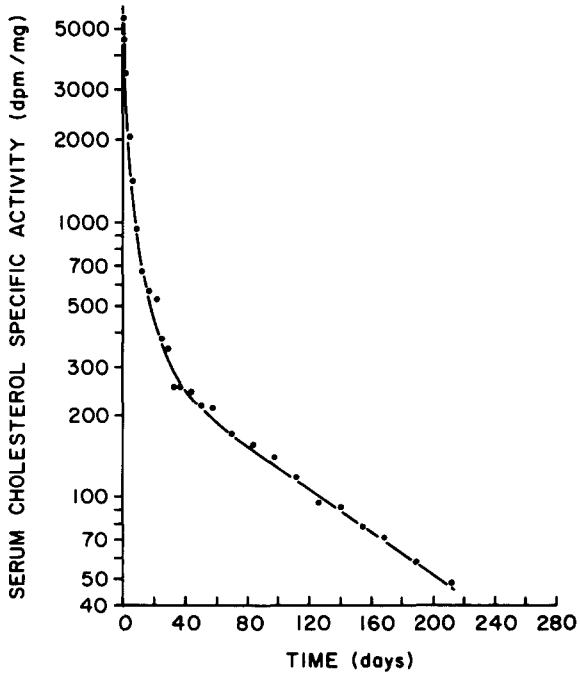

Fig. 2. Turnover of plasma cholesterol in Subject 2.

Table 3 presents the parameters of the three-pool model calculated for each of the two abetalipoproteinemic subjects.

Comparison with normal and hyperlipidemic subjects

Table 4 compares the values seen in the two abetalipoproteinemic subjects with the values predicted (for persons of the same body size and age) from the equations in Table 2, for the three major model parameters of production rate, the size of pool 1, and the minimum estimate of the size of total body exchangeable cholesterol. Because serum cholesterol level enters into the equations for pool size, and because the two subjects under study had cholesterol levels far below the range of values seen in the comparison study population, it might not be appropriate to extend the equations for pool size (developed in the study population of 82 subjects) down to cholesterol levels of 40 and 45 mg/dl. Therefore, for comparison purposes, predicted pool size estimates were calculated for three different levels of serum cholesterol: 275, 150, and either 44.6 (for subject 1) or 40.4 (for subject 2) mg/dl. These three levels represent a high serum cholesterol level (we have used, as a working definition of hypercholesterolemia (9), levels in excess of 275 mg/dl); a low normal level (the observed cholesterol levels in our 21 normal study subjects ranged from 134 to 272 mg/dl); and the actual very low levels observed in the abe-

TABLE 3. Model parameters in abetalipoproteinemic subjects

Model Parameter[a]	Subject 1	Subject 2
PR (g/d)	0.82	0.89
M_1 (g)	9.2	8.4
k_{12} (d^{-1})	0.079	0.171
k_{21} (d^{-1})	0.118	0.121
K_{13} (d^{-1})	0.013	0.021
k_{31} (d^{-1})	0.016	0.112
M_2 min (g)	13.8	6.0
M_3 min (g)	11.0	45.8
M_2 max (g)	21.5	10.0
M_3 max (g)	57.9	79.4
M_{tot} min (g)	34.0	60.2
M_{tot} inter (g)	47.6	88.4

[a] See footnote *a*, Table 2, and text for definitions of symbols and parameters. M_2 max and M_3 max = maximum estimates of the sizes of pools 2 and 3. M_{tot} inter = estimate for total body exchangeable cholesterol computed by assuming that half of body cholesterol synthesis occurs in pool 1, and half (evenly divided) in pools 2 and 3.

TABLE 4. Comparison of observed and predicted[a] model parameters

	PR	M_1	M_{tot} min
	g/d	*g*	*g*
A. Subject 1			
Observed values	0.82	9.2	34.0
Predicted for Chol 275	0.70 (0.27)[b]	18.9 (2.6)	57.2 (9.3), 57.5 (9.4)
Predicted for Chol 150	0.70 (0.27)	13.9 (2.7)	45.8 (9.6), 50.7 (9.2)
Predicted for Chol 44.6	0.70 (0.27)	9.7 (2.9)	36.2 (10.0), 45.0 (9.8)
B. Subject 2			
Observed values	0.89	8.4	60.2
Predicted for Chol 275	0.96 (0.27)	22.7 (2.6)	69.6 (9.1), 79.9 (9.2)
Predicted for Chol 150	0.96 (0.27)	17.7 (2.6)	58.2 (9.3), 71.4 (9.4)
Predicted for Chol 40.4	0.96 (0.27)	13.3 (2.8)	48.3 (9.7), 63.9 (9.8)

[a] Predicted values were obtained from the appropriate equation (or equations, for M_{tot} min) given in Table 2.

[b] The values in parentheses are the standard deviations of the predicted values, estimated from the residual error values around the regression equation (for that parameter) in the comparison study population of 82 subjects.

talipoproteinemic subjects. The predicted values for M_{tot} min (for each cholesterol level) were calculated from each of the two equations shown for this model parameter in Table 2; both values (equation 1; equation 2) are listed in Table 4.

The values for cholesterol PR observed for the two abetalipoproteinemic subjects (0.82 and 0.89 g/day) were close to the values predicted for persons of their body weight (see Table 4). Thus, the total body turnover rate of cholesterol appeared to be quite normal in both subjects studied.

In contrast, very low values were obtained for M_1, the size of pool 1, in both abetalipoproteinemic subjects. The values (9.2 g and 8.4 g) were both below the lowest value (12.7 g) actually observed in our comparison study population of 82 subjects. They were also well below the values predicted for normal persons of this size with low cholesterol levels (of 150 mg/dl, see Table 4), about 1.7 standard deviations below the prediction for subject 1, and 3.6 standard deviations below that for subject 2. Thus, the qualitative finding in the 82 subjects that the size of pool 1 decreased with decreasing levels of serum cholesterol appeared to remain valid even at the very low serum cholesterol levels in the two subjects under study. The observed very low values for M_1 in the abetalipoproteinemic subjects are consistent with the expectation from the comparison study population that M_1 should be very low in these two subjects.

The plasma content of cholesterol was estimated as 1.02 g and 1.16 g, for subjects 1 and 2, respectively, by assuming plasma volumes equivalent to 4.5% of the body weight. Thus, the extra-plasma mass of cholesterol in pool 1 could be estimated at 8.2 g and as 7.2 g, for the two subjects, respectively.

For subject 1, the estimated value for total body exchangeable cholesterol (M_{tot} min) was also low. The value for subject 2, however, fell within the two values predicted from the two regression equations, for a normal person of her size with low cholesterol level. The observed values for the two subjects were also compared (see Table 4) to the values that one would predict by extrapolating the regression equations for M_{tot} min down to 44.6 mg/dl (for 1) or to 40.4 mg/dl (for 2). The value for 1 was slightly below but close to the predicted values, while that for 2 fell near the upper of the two values predicted from the two equations. Thus, these two subjects neither prove nor disprove the applicability to abnormally low serum cholesterol levels of our earlier finding that total body exchangeable cholesterol decreases with decreasing serum cholesterol level.

DISCUSSION

Two general experimental approaches have been used in recent years to investigate the in vivo parameters of body cholesterol metabolism in intact humans. In one of these, the sterol balance method, the daily turnover of cholesterol (in g/day) is determined directly by measurement of the fecal excretion products of cholesterol (fecal neutral sterols and bile acids) (18). The second, kinetic, approach has involved analysis of the turnover of plasma cholesterol following the injection of radioactively labeled cholesterol or a biosynthetic precursor of cholesterol (9, 14, 15, 19). Estimates of the daily turnover of cholesterol obtained from kinetic studies agree well with estimates of this parameter determined by simultaneous sterol balance studies (8, 18). Some investigators have also used combinations of kinetic and sterol balance experiments in particular studies (8, 18).

The studies reported here were conducted in order to obtain information about the parameters of whole body cholesterol metabolism in patients with abetalipoproteinemia by means of long-term kinetic studies. Previous studies of cholesterol synthesis and turnover rates in such patients have all employed sterol balance techniques (4–7). These previous studies have reported that abetalipoproteinemic patients displayed either relatively normal (4, 5), or only moderately elevated (6, 7) cholesterol synthesis and turnover rates. In general, these previous studies have agreed that in vivo cholesterol synthesis in abetalipoproteinemia seems to be down regulated in a fairly effective manner.

The results reported here confirm and extend this conclusion. With the three-pool model used, cholesterol production rate (PR) is equivalent to the total body turnover rate (15). Both abetalipoproteinemic subjects showed values for cholesterol PR that were similar to those expected for persons of their body weight. In both normal and hyperlipidemic subjects, the major determinant of cholesterol PR is body weight alone (9) (see also Table 2). No function of serum lipid levels significantly influenced PR in our comparison study population of 82 subjects. The results indicate that total body cholesterol turnover in the two abetalipoproteinemic patients appeared to be regulated in a manner similar to that seen in normal and hyperlipidemic subjects. It should be noted that in normal and hyperlipidemic subjects PR comprises both newly biosynthesized cholesterol and exogenous cholesterol absorbed into the body (assumed, in previous studies (9, 15), to be 0.2 g/day). Since patients with abetalipoproteinemia manifest fat malabsorption, it is likely that the PR values obtained for the two patients studied here almost entirely represent daily cholesterol synthesis rates.

Cholesteryl ester and apoE-rich HDL appear to play an important role in the regulation of cholesterol synthesis in patients with abetalipoproteinemia (13). These apoE-rich lipoproteins are able to deliver significant amounts of cholesterol to tissues via the LDL receptor pathway, and can account for the finding, confirmed here, that cholesterol synthesis rates are not derepressed in patients with abetalipoproteinemia.

The same three-pool model used before (9, 15) provided the best fit to the long-term data in each of the two abetalipoproteinemic subjects. As discussed above, this finding extends our previous conclusion (9) that the three-pool model appears to be generally valid for the study of cholesterol turnover in humans.

Both patients showed extremely low values for M_1, the size of pool 1. As discussed before (15), pool 1, which consists of cholesterol in fairly rapid equilibrium with plasma cholesterol, normally consists mainly of cholesterol in plasma, blood cells, liver, and intestines. The results obtained here suggest that these tissues may have unusually low concentrations of cholesterol in patients with abetalipoproteinemia. This is not simply a matter of a smaller mass of cholesterol in the plasma compartment, since plasma cholesterol normally comprises only a small fraction of the mass of cholesterol in pool 1. It must be recognized, of course, that the three pools in the model represent mathematical constructs and do not have precise physical meaning (9, 15). Moreover, we do not know whether the cholesterol molecules in the same tissues that comprise pool 1 in normal persons will also be in rapid equilibrium with plasma cholesterol (and hence be part of pool 1) in abetalipoproteinemic patients. However, the finding that total body exchangeable cholesterol was also low (or low normal) in these patients suggests that the very low values observed for M_1 were not due to a redistribution of cholesterol usually found in pool 1 into other pools of the model. Accordingly, we tentatively conclude that the major tissues that comprise pool 1 (e.g., liver, intestines) may have low cholesterol levels in abetalipoproteinemia. Direct analytic data on these and other tissues from abetalipoproteinemic patients would be of great interest.

Some difference was observed between the two patients with regard to the observed estimates for total body exchangeable cholesterol. Thus, with subject 1, the observed value for M_{tot} min was very low, although not significantly below the predicted values for a person of his size (Table 4). With subject 2, the observed estimate for total body exchangeable cholesterol was well within the range of values predicted for persons of her size, with low to extremely low cholesterol levels. Part of the difference between the two subjects may relate to the fact that subject 1 is a slim man, with excess weight of −7.2 kg, whereas subject 2 has much more adipose tissue, with excess weight of 10.8 kg. Adipose tissue cholesterol has been found to be an important part of the most slowly turning over compartment, pool 3 (20). These differences in body size and adiposity may have contributed, in part, to the differences observed between the two patients with regard to the estimates of the size of pool 3 and of total body exchangeable cholesterol.

The finding in abetalipoproteinemia of a normal rate of body cholesterol turnover, together with a very small mass of cholesterol in pool 1, is intriguing. There is evidence that, in subhuman primates, most of body cholesterol synthesis occurs in the tissues that comprise the rapidly exchanging compartment, pool 1 (21, 22). The present results suggest that much of the exchangeable cholesterol normally in pool 1 does not influence cholesterol synthesis rates in the tissues that comprise this pool. Since abetalipoproteinemic patients presumably have reasonably normal cholesterol delivery rates to their tissues via apoE-rich HDL (13), the results suggest that

cholesterol delivered to cells via lipoproteins and lipoprotein receptors plays a particularly critical role in the regulation of cholesterol biosynthesis. This conclusion is consistent with information available about the role of the LDL receptor pathway in the regulation of cholesterol homeostasis within cells (11). Much of the exchangeable cholesterol in cells (e.g., in various membrane fractions) probably exists in metabolic compartments relatively removed from that compartment of cholesterol that is directly involved in the regulation of cholesterol biosynthesis within the cell.

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